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Consumption of Black Tea and Cancer Risk: a Prospective Cohort Study

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Background: **Tea is one of the most frequently consumed beverages in the world. Antioxidant polyphenol compounds (such as catechins and flavonols) are abundantly present in both green and black teas and have been observed to have anticarcinogenic properties in cell and animal model studies. In black tea, however, most of the catechins have been oxidized to forms that may have reduced anticarcinogenic properties. Despite indications from experimental studies that tea may protect against cancer, epidemiologic evidence has been inconclusive.** ***Purpose:*** **The association between black tea consumption and the subsequent risk of stomach, colorectal, lung, and breast cancers was investigated in The Netherlands Cohort Study on Diet and Cancer among 58 279 men and 62 573 women aged 55-69 years.** ***Methods:*** **Subjects in the cohort completed a self-administered questionnaire on dietary habits and other risk factors for cancer at base line in 1986. Follow-up for cancer was done by means of computerized record linkage with all nine regional cancer registries in The Netherlands and the national pathology database. During 4.3 years of follow-up, 200, 650, 764, and 650 cases of stomach, colorectal, lung, and breast cancers were diagnosed, respectively. The questionnaire data of case subjects and those of a random subcohort (n = 3500) were used to calculate rate ratios (RRs) of cancer in categories of consumers of black tea compared with nonconsumers.** ***Results:*** **Tea was not used by 13% of the subjects in the cohort, whereas 37%, 34%, and 16% consumed one to two, three to four, and five or more cups of tea per day, respectively. No association was observed between tea consumption and risk of colorectal cancer: The risk among tea drinkers in each consumption category was similar to that among nondrinkers. The RR of breast cancer among consumers of five or more cups of tea per day was 1.3 (95% confidence interval = 0.9-2.0); no dose–response association was observed. In age- and sex-adjusted analyses, consumption of tea was inversely associated with stomach (two-sided *P* for trend = .147) and lung (two-sided *P* for trend <.001) cancers. However, tea drinkers appeared to smoke less and to eat more vegetables and fruits than nondrinkers. When smoking and dietary factors were taken into account, tea in itself did not appear to protect against stomach and lung cancers: The RRs in all consumption categories were close to unity. Analysis of the tea and cancer relationship in a subgroup that included subjects in the lowest two quintiles of consumption of vegetables and fruits also failed to reveal a protective effect of tea consumption on the risk of three cancer types studied (colorectal, lung, and breast cancers).** ***Conclusions:*** **This investigation does not support the hypothesis that consumption of black tea protects against four of the major cancers in humans; a cancer-enhancing effect was not evident, either. [J Natl Cancer Inst 1996;88:93-100]**

Tea (*Camellia sinensis*) is one of the most frequently consumed beverages. About 20% of the world production is consumed as green tea, an extract from heated and dried tea leaves, whereas 80% is consumed as black tea, which is produced from leaves by enzymatic oxidation. Dried tea extract contains 25%-40% polyphenols; in green tea, these are flavonols (catechins), of which epigallocatechingallate is the most prevalent compound (*1,2*). In black tea, most of the catechins are oxidized to thearubigens and theaflavins, which give the extract its characteristic red–brown color. Both green tea and black tea also contain flavonol glycosides (quercetin and kaempferol) (*1,3*).

Much experimental research has been conducted on the anticarcinogenic properties of mostly green tea extracts and their major constituents (*4,5*). Although some cancer-enhancing properties of green and black tea have been described (*4*), most research has been done on inhibiting effects of catechins, other polyphenols, and tea extracts. These compounds appear to have strong antioxidant properties (*2*) and to inhibit nitrosation (*6*). Anticarcinogenic effects have been demonstrated in many animal models (*5*). Relatively little experimental research has been done on black tea extracts and thearubigens or theaflavins. One study (*7*) suggested that the anticarcinogenic properties of black tea may be somewhat weaker than those of green tea. In summary, evidence from experimental studies shows that it is very plausible that certain compounds present in green and black tea may protect against the development of at least some cancers. In contrast to experimental studies, epidemiologic studies on tea consumption and several types of cancer have yielded inconclusive results (*5,8-20*).

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See "Notes" section following "References."

The present epidemiologic study was undertaken to determine the association between black tea consumption and the risk of four types of cancer (stomach, colorectal, lung, and breast cancers). The investigation was carried out within the framework of The Netherlands Cohort Study on Diet and Cancer, a large-scale prospective cohort study that was started in 1986 among the general population and involved 58 279 men and 62 573 women aged 55-69 years. This population drinks mainly black tea at an intermediate level (650 g per capita per year), i.e., not as high as in the U.K. but much higher than in most other European countries and the United States (*4*).

Subjects and Methods

The Cohort

The Netherlands Cohort Study on Diet and Cancer was initiated in September 1986. The cohort included 58 279 men and 62 573 women aged 55-69 years at the start of the study. The study population originated from 204 municipal population registries throughout the country. At base line, the cohort members completed a mailed, self-administered questionnaire on dietary habits and other risk factors for cancer. For data processing and analysis, the case–cohort approach was used: The case subjects were enumerated for the entire cohort, while the person-years at risk accumulating in the cohort were estimated from a random sample (subcohort). This subcohort of 3500 subjects (1688 men and 1812 women) was sampled from the entire cohort in a strictly random manner immediately after base-line measurement and was followed-up for vital status over a 4.3-year period. No subcohort member was lost to follow-up. The study design has been described in detail elsewhere (*21*).

Follow-up for Cancer

Follow-up for incident cancer was established by computerized record linkage with all nine regional cancer registries in The Netherlands and with the Nationwide Pathology Database (PALGA). The method of record linkage has been described previously (*22*). This analysis is restricted to cancer incidence in the period from September 1986 (base-line measurement) through December 1990, i.e., a follow-up period of 4.3 years. During this period, completeness of follow-up of the cohort through linkage with the cancer registries and PALGA was estimated to be at least 96% (*23*). After the exclusion of subjects who reported a history of cancer other than skin cancer in the base-line questionnaire (Table 1), the following numbers of incident cases with microscopically confirmed primary invasive carcinoma were identified: 200 cases of stomach cancer (160 men and 40 women), 396 cases of colon cancer (202 men and 194 women), 254 cases of rectal cancer (159 men and 95 women), 764 cases of lung cancer (675 men and 89 women), and 650 cases of breast carcinoma (women only).

Questionnaire

The self-administered questionnaire has been described in more detail elsewhere (*24*). For this analysis, characteristics of interest are summarized below. The dietary section of the questionnaire, a 150-item, semiquantitative food-frequency questionnaire, concentrated on habitual consumption of food and beverages during the year preceding the start of the study. Regarding tea, it was asked whether the responder drank tea and, if so, how many cups per day. The type of tea used was not asked, because native Dutch people rarely drink any tea other than black tea. The questionnaire was validated against a 9-day diet record (*24*). Daily mean nutrient intakes were calculated with the use of the computerized Dutch food composition table (*25*). Energy adjustment of fat intake was done by regression analysis according to the method of Willett and Stampfer (*26*). The standard size of a cup of tea was assessed from a pilot study to be 125 mL. In The Netherlands, tea is usually brewed from 1 g tea per 100 mL water for 5 minutes. It is usually drunk without milk added and is mainly used at breakfast (40%) and between meals (43%) (*27*).

Data Analysis

Questionnaire data on all case subjects and the subcohort were entered in the computer database twice and processed in a manner blinded with respect to case–cohort status to minimize observer bias in coding and interpretation of the data. After prevalent cancer cases other than skin cancer were excluded from the subcohort, 3346 subjects (1630 men and 1716 women) remained in this group (Table 1). Furthermore, subjects with incomplete or inconsistent dietary data were excluded, according to criteria described previously (*24*) (Table 1). The question on whether they drank tea was left blank by 1.1% of the subjects; they were considered to be nonusers. Two percent of the subjects reported drinking tea but did not report how much; they were assumed to drink three cups per day (i.e., the median number of cups consumed daily by tea drinkers). For tea consumption as a continuous variable, the number of cups was multiplied by 125 mL. For tea consumption as a categorical variable, it was categorized as one, two, three, four, and five or more cups per day; noninteger values were rounded up to the nearest integer. Eventually, 1525 male and 1598 female subcohort members were included in the analysis (corresponding to an average of 6344 and 6757 person-years, respectively), together with 183, 371, 232, 676, and 605 cases of stomach, colon, rectal, lung, and breast cancers, respectively. Data were analyzed with the use of the case–cohort approach (*28*), assuming exponentially distributed survival times in the follow-up period. Since standard software was not available for this type of analysis, specific programs were developed in GLIM (Generalized Linear Interactive Modeling) (*29,30*) to account for the additional variance introduced by sampling from the cohort instead of using the entire cohort (*31*). By means of multivariate analysis, rate ratios (RRs) for tea consumption were adjusted for confounders. Apart from age and sex, confounders were considered a priori for each type of cancer specifically. For stomach cancer, the confounders considered were as follows: level of education (primary and lower vocational, secondary and medium vocational, and university and higher vocational), smoking status (never smoker, ex-smoker, and current smoker), pack-years of cigarettes smoked, family history of stomach cancer, and intakes of coffee, beta carotene, vitamin C, and alcohol. For colorectal cancer, the confounders considered were as follows: level of education (three categories), smoking status, family history of intestinal cancer, previous gallbladder surgery, body mass index, and intakes of coffee, dietary fiber, folate, beta carotene, vitamin C, and alcohol. Intakes of energy, fat, red meat, and calcium were not considered as confounders for colorectal cancer, since we showed previously that they were not associated with this cancer (*32,33*). For lung cancer, the confounders considered were as follows: level of education (primary, lower vocational, secondary and medium vocational, and university and higher voca-

Table 1. Exclusions from subcohort and case subjects

	Total		Prevalent case subjects		Incomplete or inconsistent dietary questionnaires		Remaining for analysis	
	Men	Women	Men	Women	Men	Women	Men	Women
Subcohort	1688	1812	58	96	105	118	1525	1598
Cancer								
Stomach	175	49	15	9	16	1	144	39
Colorectal	386	306	25	17	21	26	340	263
Lung	730	107	55	18	76	12	599	77
Breast	—	705	—	55	—	45	—	605

Table 2. Distribution of tea drinking (%) in subcohort and cancer case subjects—The Netherlands Cohort Study on Diet and Cancer, 1986

	Nonconsumers		1-2 cups per day		3-4 cups per day		≥5 cups per day	
	Men	Women	Men	Women	Men	Women	Men	Women
Subcohort	14.9	11.0	40.7	32.7	31.5	37.0	12.9	19.4
Cancer								
Stomach	15.3	10.3	40.3	43.6	33.3	30.8	11.1	15.4
Colon	13.0	12.9	38.9	33.1	34.7	37.1	13.5	16.9
Rectal	13.6	14.1	36.1	27.1	30.6	41.2	19.7	17.6
Lung	21.0	14.3	39.4	44.2	25.4	33.8	14.2	7.8
Breast	—	8.6	—	31.4	—	39.3	—	20.7

tional), smoking status (never smoker, ex-smoker, and current smoker), pack-years of cigarettes smoked, family history of lung cancer, and intakes of coffee, beta carotene, and vitamin C. For breast cancer, the confounders considered were as follows: level of education (three categories), smoking status (non-smoker, current smoker), history of benign breast disease, history of breast cancer in mother and sisters, body mass index, age at menarche, age at first birth, parity, use of oral contraceptives, age at menopause, and intakes of energy, fat, alcohol, and coffee. Antioxidant vitamins were not considered, since they were not associated with breast cancer risk (van den Brandt PA: unpublished observation).

For colorectal cancer, risks were assessed for men and women separately. The number of female cases of stomach and lung cancers, however, was too small to conduct a sex-specific analysis. Since subclinical symptoms of gastrointestinal cancer might have influenced dietary habits before diagnosis, we repeated the analyses for stomach and colorectal cancers after stratification of case subjects according to their date of diagnosis; those diagnosed in the first 2 years of follow-up were compared with those diagnosed later. There is some evidence in the literature that compounds with antioxidant properties substitute for each other when a relative shortage exists (*34*). Therefore, a separate analysis was performed in a subgroup of subjects who were in the two lowest quintiles of vegetable and fruit consumption; this subgroup constituted about 20% of the total study population. The analysis was based on 127, 171, and 120 cases of colorectal, lung, and breast cancers, respectively; the total number of cases of stomach cancer was not sufficient to be included. Two-sided *P* values for tests for trend were used throughout.

Results

Table 2 shows the distribution of tea drinking for subcohort and cancer case subjects. Eighty-five percent of the male and 89% of the female subcohort members reported that they drink tea. The average daily consumption among tea drinkers was 321 mL for men and 383 mL for women. The highest proportion of subjects who did not drink tea was found among lung cancer case subjects (21% in men and 14% in women), whereas only 9% of the breast cancer case subjects did not drink tea compared with 11% of the female subcohort members.

Tea drinking was associated with many potential confounders for the four cancer types (Table 3). The strongest positive associations were observed with the following: age; sex (women drank more tea); consumption of vegetables and fruit; intakes of fiber, vitamin C, and beta carotene; and education. The strongest negative associations were found with consumption of coffee, body mass index (in particular for women), and smoking.

Table 4 presents the RRs of the four cancer types for consumption of an increasing number of cups of tea per day compared with nondrinkers of tea. For stomach cancer, a weak (nonsignificant) inverse association was observed for the age- and sex-adjusted data, but this association disappeared completely after adjustment for education, smoking status, family history, and intakes of coffee and vitamin C. Coffee consumption was the only confounder that changed the estimated RRs by more than 0.1. Additional inclusion of pack-years of cigarettes smoked and beta carotene and alcohol intakes in the model did not change the reported RRs. Stratification according to follow-up time showed a weak, nonsignificant inverse trend for tea and stomach cancer during the first 2 years (RRs of 1.1, 0.9, 0.7, 0.8, and 0.7 in the respective categories of tea consumption) and a slightly positive association during subsequent follow-up years (RRs of 1.1, 1.4, 1.5, 1.3, and 1.2).

For colorectal cancer, neither the age- and sex-adjusted RRs nor the multivariate RRs showed any association. Stratification of case subjects according to year of follow-up resulted in similar RRs for both follow-up periods. Sex- and site-specific results for colorectal cancer are shown in Table 5. Multivariate RRs, which were similar to the age-adjusted RRs, appeared to differ between colon and rectal cancers and between men and women. Women who drank tea had a nonsignificant lower risk for colon as well as rectal cancers, but a dose–response effect was not observed. For men, the site-specific results did not show a consistent pattern. Altogether, the observed differences appeared to be within the limits of expected variation.

For lung cancer, the age- and sex-adjusted data showed a statistically significant inverse association (P for trend <.001) with an increasing number of cups consumed per day (Table 4). However, this association disappeared completely after adjustment for confounders; smoking status and pack-years of cigarettes smoked adjusted the RRs by more than 0.1. Coffee consumption was not included in the model, since it did not affect the RRs.

Table 4 also shows the results for breast cancer. Regardless of the quantity of tea consumed per day, all tea drinkers had a slightly higher risk than nondrinkers (RR = 1.3; 95% confidence interval = 0.9-2.0 in the group drinking five or more cups per day), but no trend with increasing consumption was observed. Adjustment for confounders barely affected the estimated RRs. Further adjustment for coffee consumption had no effect.

The analyses in subgroups with low vegetable and fruit consumption showed no strikingly different results (Table 6). For colorectal cancer, the association was similar to that in the total group. For lung cancer, the RRs were 0.7 and 0.6 in the categories of one to two cups per day and three to four cups per day, respectively, but 1.1 in those who drank five or more cups per day. The risk of breast cancer appeared to be higher in tea drinkers than in the total group (RRs of 2.1, 1.5, and 2.0 for one

Table 3. Mean intake of tea (mL/day)* across categories of several characteristics of the subcohort—The Netherlands Cohort Study on Diet and Cancer, 1986

Characteristic	Men	Women
Age, y		
55-59	281	356
60-64	322	393
65-69	377	409
Energy†		
Q1	306	320
Q5	332	417
Fat, energy-adjusted†		
Q1	356	398
Q5	311	360
Dietary fiber†		
Q1	277	337
Q5	359	434
Vitamin C†		
Q1	254	333
Q5	357	407
Beta carotene†		
Q1	277	356
Q5	325	394
Alcohol		
Nonusers	347	383
≥30 g/day	288	367
Coffee, cups/day		
0-2	425	498
≥7	212	254
Vegetables		
Q1	292	357
Q5	332	376
Fruit		
Q1	290	366
Q5	351	402
Body mass index, kg/m^2		
≤22	334	404
≥27	311	345
Smoker		
Never smoker	353	404
Ex-smoker	336	387
Current smoker	297	320
Education		
Primary	304	362
Secondary	331	402
University	342	410
Cholecystectomy		
No	319	379
Yes	374	402
FH of stomach cancer‡		
No	320	383
Yes	339	381
FH of intestinal cancer‡		
No	320	384
Yes	337	365
FH of lung cancer‡		
No	322	384
Yes	316	371
FH of breast cancer, mother‡		
No	—	382
Yes	—	414
FH of breast cancer, sisters‡		
No	—	386
Yes	—	329
Parity		
Nulliparous	—	392
1-2 children	—	385
≥3 children	—	381
Age at first birth, y		
≤24	—	370
≥30	—	367
Age at menarche, y		
≤12	—	408
≥15	—	362
Age at menopause, y		
≤49	—	373
≥50	—	393
Oral contraceptive use		
Never	—	389
Ever	—	363
Benign breast disease		
No	—	381
Yes	—	405

*Reported number of cups consumed per day multiplied by 125 mL.
†Q1 = lowest quintile; Q5 = highest quintile.
‡FH = family history.

to two, three to four, and five or more cups per day, respectively), but none of the RRs differed significantly from unity, and the trend was not statistically significant.

Discussion

In this population, the consumption of black tea appears to be inversely associated with some risk factors for cancer, such as smoking and a reduced consumption of vegetables and fruits. Both factors are strong confounders for stomach and lung cancers. Thus, adjustment for smoking, vitamin C, and, to a lesser extent, beta carotene removed the initially inverse associations between tea consumption and both stomach and lung cancers, indicating that the protective effect was not attributable to tea itself. For colorectal and breast cancers, for which no such strong confounders were identified, no consistent association with tea consumption was observed. We also observed no associations in a subgroup of the cohort with the lowest consumption of vegetables and fruits, indicating that the ineffectiveness of tea does not seem to depend on the level of intake of other antioxidants. The increased risk (without evidence of a dose response) observed for breast cancer among tea drinkers in this subgroup is difficult to interpret.

Although we could not entirely exclude that the absence of an association was explained by an uncontrolled confounder (e.g., physical activity for colon cancer), we controlled for the most important known confounders. It was not possible to include in the analyses the intake of vitamin E and the use of vitamin supplements, which is rather low in The Netherlands. Their effect on cancer, if any, and their association with tea consumption are

Table 4. Relationship between tea consumption and risk of cancer—The Netherlands Cohort Study on Diet and Cancer, 1986-1990

	Tea consumption, cups/day						
	Nonconsumer*	1	2	3	4	≥5	*P* for trend
Stomach cancer							
No. of case subjects/subcohort†	26/398	24/377	51/759	27/474	32/591	22/503	
Rate ratio, age- and sex-adjusted	1.00	1.02	1.00	0.88	0.84	0.71	.147
Rate ratio, multivariate‡	1.00	1.10	1.13	1.05	1.02	0.94	.728
95% confidence interval	—	0.61-1.98	0.68-1.87	0.59-1.88	0.58-1.79	0.51-1.75	
Colorectal cancer							
No. of case subjects/subcohort†	75/381	75/359	124/714	87/451	111/551	92/473	
Rate ratio, age- and sex-adjusted	1.00	1.07	0.84	0.91	0.97	0.95	.742
Rate ratio, multivariate§	1.00	1.04	0.85	0.94	0.95	0.94	.748
95% confidence interval	—	0.72-1.50	0.62-1.18	0.66-1.33	0.68-1.33	0.66-1.34	
Lung cancer							
No. of case subjects/subcohort†	114/379	75/362	166/726	76/447	88/562	81/483	
Rate ratio, age- and sex-adjusted	1.00	0.65	0.71	0.51	0.49	0.60	<.001
Rate ratio, multivariate‖	1.00	0.93	1.01	0.84	0.90	1.07	.910
95% confidence interval	—	0.64-1.36	0.72-1.41	0.56-1.26	0.62-1.31	0.73-1.57	
Breast cancer (female)							
No. of case subjects/subcohort†	45/153	52/136	110/313	80/219	113/286	107/269	
Rate ratio, age-adjusted	1.00	1.30	1.19	1.23	1.32	1.33	.146
Rate ratio, multivariate¶	1.00	1.30	1.15	1.18	1.29	1.31	.185
95% confidence interval	—	0.81-2.09	0.76-1.74	0.76-1.83	0.85-1.95	0.86-1.99	

*Reference group.

†Number of subjects does not add up to the total number because of missing values for covariates.

‡Further adjusted for education (primary and lower vocational, secondary and medium vocational, and university and higher vocational), smoking status (never smoker, ex-smoker, and current smoker), family history of stomach cancer, and intake of coffee and vitamin C.

§Further adjusted for family history of intestinal cancer, body mass index, gallbladder surgery, and intake of fiber, folate, alcohol, and coffee. Education, smoking status, and intakes of vitamin C and beta carotene were not required for adjustment.

‖Further adjusted for education (primary, lower vocational, secondary and medium vocational, and university and higher vocational), smoking status (never smoker, ex-smoker, and current smoker), pack-years of cigarettes smoked, family history of lung cancer, and intakes of beta carotene and vitamin C.

¶Further adjusted for benign breast disease, history of breast cancer in mother and sisters, age at menarche, age at menopause, use of oral contraceptives, age at first birth, parity, body mass index, smoking status (nonsmoker, current smoker), education (primary and lower vocational, secondary and medium vocational, and university and higher vocational), and intakes of energy, fat, and alcohol.

expected to be in the same direction as the other antioxidant vitamins (vitamin C and beta carotene). It is, therefore, not very likely that confounding could explain these results.

Circumstances other than the absence of an effect may explain the results (e.g., chance). However, the power of the study was quite large, except for stomach cancer and the sex- and site-specific analyses of colorectal cancer, which may have been influenced somewhat by chance. Another argument may be the potential instability of tea drinking over time. The food-frequency questionnaire formally referred to the dietary habits in the year preceding the base-line measurement. Since cancer has a long induction period, dietary habits directly preceding the manifestation of cancer may have nothing to do with its development. We have shown, however, that, in general, the questionnaire represents a subject's dietary habits over a much longer period (*35*). The 1987-1988 and the 1992 Dutch Food Consumption Surveys (*36,37*) provided evidence that the increase in tea consumption with age is due to a combination of aging (people tend to drink more tea as they grow older) and generation effects (earlier generations drink more tea). Presum-

Table 5. Tea drinking and rate ratios (RRs)* of colon and rectal cancers for men and women separately

	Men				Women			
	Colon cancer (n = 184)		Rectal cancer (n = 140)		Colon cancer (n = 163)		Rectal cancer (n = 73)	
Tea drinking, cups/day	RR	95% confidence interval (CI)	RR	95% CI	RR	95% CI	RR	95% CI
Nonconsumer†	1.00	—	1.00	—	1.00	—	1.00	—
1	1.43	0.80-2.57	1.05	0.54-2.04	0.75	0.37-1.54	0.65	0.23-1.86
2	0.89	0.52-1.55	0.76	0.41-1.39	1.01	0.57-1.78	0.64	0.27-1.52
3	1.13	0.63-2.04	0.77	0.38-1.53	0.93	0.50-1.72	0.75	0.30-1.86
4	1.07	0.60-1.92	1.04	0.55-1.97	0.83	0.46-1.52	0.85	0.36-1.98
≥5	1.01	0.53-1.91	1.49	0.78-2.85	0.69	0.37-1.29	0.71	0.29-1.72
P for trend	.796		.212		.264		.849	

*Adjusted for age, family history of intestinal cancer, body mass index, gallbladder surgery, and intakes of fiber, folate, alcohol, and coffee.

†Reference group.

Table 6. Relationship between tea consumption and risk of cancer in the two lowest quintiles of vegetable and fruit consumption—The Netherlands Cohort Study on Diet and Cancer, 1986-1990

	Tea consumption, cups/day				
	Nonconsumer*	1-2	3-4	≥5	*P* for trend
Colorectal cancer					
No. of case subjects/subcohort†	21/84	49/223	39/172	18/84	
Rate ratio, multivariate‡	1.00	0.84	0.89	0.96	.982
95% confidence interval	—	0.45-1.55	0.47-1.69	0.45-2.11	
Lung cancer					
No. of case subjects/subcohort†	41/86	68/232	39/177	23/84	
Rate ratio, multivariate§	1.00	0.72	0.62	1.08	.852
95% confidence interval	—	0.40-1.31	0.31-1.24	0.49-2.38	
Breast cancer, female					
No. of case subjects/subcohort†	10/38	51/98	33/90	26/52	
Rate ratio, multivariate‖	1.00	2.06	1.47	2.00	.392
95% confidence interval	—	0.85-4.95	0.59-3.68	0.77-5.20	

*Reference group.

†Number of subjects does not add up to the total number because of missing values for covariates.

‡Adjusted for age; sex; family history of intestinal cancer; body mass index; gallbladder surgery; and intakes of fiber, folate, alcohol, and coffee.

§Adjusted for age, sex, education (primary, lower vocational, secondary and medium vocational, and university and higher vocational), pack-years of cigarettes smoked, family history of lung cancer, and intakes of beta carotene and vitamin C.

‖Adjusted for age, benign breast disease, history of breast cancer in mother and sisters, age at menarche, age at menopause, use of oral contraceptives, age at first birth, parity, body mass index, smoking status (nonsmoker, current smoker), education (primary and lower vocational, secondary and medium vocational, and university and higher vocational), and intakes of energy, fat, and alcohol.

ing that the slight increase in tea consumption during aging affects all subjects, substantial attenuation of the estimated risks due to instability of tea drinking is unlikely. Inaccuracy of recall of tea consumption as such also may be a source of attenuation of RRs. Unfortunately, we had no separate data on tea available from the validation study of our food-frequency questionnaire. Considering the simplicity of the question on tea and the small number of blanks encountered, we would expect that the accuracy of recall was better than average.

The stability of dietary habits in general does not exclude that subjects with subclinical cancer, in particular gastrointestinal cancer, may have changed their diet because of symptoms of the not yet diagnosed disease. For example, they may no longer tolerate some foods or beverages. Stratification according to follow-up time showed that case subjects with stomach cancer tended to decrease tea consumption in the 2 years prior to diagnosis. Thus, a preventive effect of tea on stomach cancer is even more unlikely. For colorectal cancer, no differential effects were observed for the two follow-up periods.

Epidemiologic studies on tea and many types of cancer up to those published in 1992 were reviewed by Yang and Wang (*5*). Leaving ecological studies aside, most studies were case–control studies. The investigators concluded that a protective effect of tea (green and black) was not apparent for bladder, esophageal, and kidney cancers. For esophageal cancer, a positive association was observed in several studies, but this was attributed to the temperature of the tea rather than to the tea itself. Recently, however, a large, well-conducted case–control study in Shanghai, China, observed a protective effect of green tea consumption after adjustment for smoking habits and alcohol consumption, in particular among women (*38*). Two of 13 studies on pancreatic cancer showed an inverse association. Yang and Wang (*5*) found no associations between breast cancer and black tea in the five studies reviewed; this finding was confirmed by a very large case–control study in Denmark (*8*). For colon and rectal cancers, positive, negative, and no associations were observed in a total of 11 studies. The studies reporting a negative association investigated green tea. Published studies on black tea showed no association in Denmark (*9*) and Italy (*10*) and a positive association between black tea and colon cancer in Japanese women (*11*). Stomach cancer was not found to be associated with green or black tea consumption in most of the 11 studies reviewed; positive (with green and black tea) and negative (with green tea) associations were observed in two studies each (*5*). Recent case–control studies were conducted in Japan, in which no association with green tea consumption was established (*12,13*), and in Sweden, where an inverse association of black tea consumption with stomach cancer was observed (*28*). In contrast to our findings, the investigators of the latter study stated that this association decreased but did not disappear after adjustment for confounders, including vegetable and fruit consumption. For lung cancer, four case–control and two cohort studies (*15-17*) were published altogether; most of these did not observe an association with green or black tea, except for one case–control study in Hong Kong (*18*) and a cohort study in London (*19*), both of which found a positive association. This latter study, one of the two published cohort studies that have investigated a number of cancer sites at the same time (*19,20*), differs from other studies in western societies in that tea drinking followed the same social pattern in the U.K. as coffee drinking in other countries and was more associated with unhealthy habits such as smoking. The positive associations between tea and lung and stomach cancers observed in the British study might have resulted from residual confounding. The other cohort study (*20*), conducted in Hawaii, observed no associations between (a rather low) black tea consumption and stomach, lung, and colon cancers but found an unexplained positive association for rectal cancer. Altogether, results did not

seem to differ systematically between green and black tea. Interpretation of many studies is hampered by the possibility that recall and selection bias (in case–control studies) or insufficient control of confounders influenced the results. Also, tea consumption was sometimes too low to find a meaningful effect (e.g., Italy and the United States). We believe, therefore, that the results of this large investigation, conducted prospectively on four major cancers in a male and female population with good contrast in tea consumption, make a relevant contribution to the evidence about the role of black tea in cancer.

In conclusion, this investigation does not support the hypothesis that consumption of black tea contributes to the protection against cancer occurring in humans at older ages. The question remains as to why seemingly convincing evidence for a protective effect of tea from experimental research does not emerge in epidemiologic studies. It may be that the quantity and the strength of the tea are not sufficiently high. It is more likely that most cancers in humans are not caused by the types of carcinogenic insults that tea seems to protect against in experimental research or that the relevant tea constituents are not in the right place in the body at the right moment, although tea polyphenols appear to be absorbed (*39*). We cannot, therefore, exclude that, under particular circumstances, tea protects against very specific cancers [e.g., esophageal cancer (*38*)]. Finally, the lower content of catechins in black tea may explain the absence of an effect, although epidemiologic studies on green tea were not convincing either.

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Notes

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Loss of Functional Beta$_2$-Microglobulin in Metastatic Melanomas From Five Patients Receiving Immunotherapy

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Background: **In a subset of patients with metastatic melanoma, T lymphocytes bearing the cell-surface marker CD8 (CD8$^+$ T cells) can cause the regression of even large tumors. These antitumor CD8$^+$ T cells recognize peptide antigens presented on the surface of tumor cells by major histocompatibility complex (MHC) class I molecules. The MHC class I molecule is a heterodimer composed of an integral membrane glycoprotein designated the α chain and a noncovalently associated, soluble protein called beta$_2$-microglobulin (β_2m). Loss of β_2m generally eliminates antigen recognition by antitumor CD8+ T cells.** ***Purpose:*** **We studied the loss of β_2m as a potential means of tumor escape from immune recognition in a cohort of patients receiving immunotherapy.** ***Methods:*** **We successfully grew 13 independent tumor cell cultures from tumor specimens obtained from 13 patients in a cohort of 40 consecutive patients undergoing immunotherapy for metastatic melanoma and for whom tumor specimens were available. These cell lines, as well as another melanoma cell line (called 1074mel) that had been derived from tumor obtained from a patient in a cytokine–gene therapy study, were characterized in vitro cytofluorometrically for MHC class I expression and by northern and western blot analyses for messenger RNA (mRNA) and protein expression, respectively, and ex vivo by immunohistochemistry.** ***Results:*** **After one melanoma cell line (1074mel) was found not to express functional β_2m by cytofluorometric analysis, four (31%) of the 13 newly established melanoma cell lines were found to have an absolute lack of functional MHC class I expression. Northern blot analysis of RNA extracted from the five cell lines exhibiting no functional MHC class I expression showed that these cells contained normal levels of α-chain mRNA but variable levels of β_2m mRNA. In addition, no immunoreactive β_2m protein was detected by western blot analysis. When human β_2m was transiently expressed with the use of a recombinant vaccinia virus, cell-surface MHC class I expression was reconstituted and the ability of these five cell lines to present endogenous antigens was restored. Immunohistochemical staining of tumor sections revealed a lack of immunoreactive MHC class I in vivo, supporting the notion that the in vitro observations were not artifactual. Furthermore, archival tumor sections obtained from patients prior to immunotherapy were available from three patients and were found to be β_2m positive. This result was consistent with the hypothesis that loss of β_2m resulted from immunotherapy.** ***Conclusions:*** **These data suggest that the loss of β_2m may be a mechanism whereby tumor cells can acquire immunoresistance. This study represents the first characterization of a molecular route of escape of tumors from immune recognition in a cohort of patients being treated with immunotherapy. [J Natl Cancer Inst 1996;88:100-8]**

A subset of T lymphocytes bearing the cell-surface marker CD8 can be shown to directly lyse tumor cells in vitro (*1,2*). These T cells, designated CD8$^+$ T cells, can be expanded to large numbers ex vivo and adoptively transferred back to patients together with interleukin 2 (IL-2) where they can, in some cases, effect the regression of even large tumors (*3-5*). In patients with a number of different human malignancies, antitumor T cells can be elicited that are capable of recognizing autologous tumor cells as measured by cytolytic- and cytokine-

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